Article type : Clinical Observations in Hepatology

Liver Stiffness Measurements in Patients with Non-cirrhotic Portal Hypertension – The Devil is In the Details

Raj Vuppalanchi, Karan Mathur, Maximillian Pyko, Niharika Samala, Naga Chalasani

Corresponding Author

Raj Vuppalanchi, MD

Associate Professor of Medicine

702 Rotary Circle, Suite 225

Division of Gastroenterology

Indiana University School of Medicine

Indianapolis, IN 46202

Email: rvuppala@iu.edu

Phone: 317-278-1652

Fax: 317-278-1949

Key Words: Nodular regenerative hyperplasia, portal hypertension, Fibroscan

Short Title: Transient elastography for evaluation of non-cirrhotic portal hypertension

Conflict of Interest: No conflict of interest

Introduction

Non-cirrhotic portal hypertension (NCPH) is often a diagnostic challenge due to signs and symptoms of portal hypertension that overlap with cirrhosis. The etiology of NCPH is broadly classified as prehepatic, hepatic (pre-sinusoidal and sinusoidal) and post-hepatic.[1] Some common etiologies of NCPH encountered in clinical practice include portal vein thrombosis (prehepatic) and nodular regenerative hyperplasia (NRH) (hepatic). Liver histology, although considered gold standard to exclude cirrhosis in individuals with suspected NCPH, is often limited by subtle histologic features or inadequate sampling. Liver stiffness measurements (LSM) by vibration-controlled transient elastography (VCTE) may provide clinically important information to distinguish NCPH from cirrhosis by revealing normal LSM in prehepatic and presinusoidal NCPH.

Clinical Observation

Forty-three patients with a diagnosis of NCPH based on clinical, radiologic, histologic and portal pressure measurements, also underwent VCTE using Fibroscan 502 Touch for LSM. Cirrhosis was excluded by histology in 88% (38/43) of the cohort. The common etiologies of NCPH in the cohort were drug-induced NRH (51%) and portal vein thrombosis (30%). Esophageal and/or gastric varices were present in 74% of the cohort. In patients with NCPH, LSM correlated significantly with wedge hepatic vein pressure (r=0.48, p-value = 0.006) and HVPG (r=0.6, p-value = <0.001). Table 1 shows selected clinical and laboratory characteristics and portal pressure measurement. The proportion of patients with abnormal LSM indicative of compensated advanced chronic liver disease (>10kPa) as defined by Baveno VI was lowest at 31% in PVT as compared to 50% and 75% in NRH and miscellaneous categories of NCPH respectively (Figure 1). Among the 13 cases with PVT, 11 underwent portal pressure measurements; of these 5 had abnormal LSM (45%). In those with abnormal LSM, the free hepatic vein pressure was significantly higher 11 ± 3 vs. 6 ± 4 mm Hg (p-

value = 0.033). Otherwise, right atrial pressure, wedge hepatic vein pressure and hepatic vein pressure gradient were not different between PVT patients with normal and abnormal LSM. The LSM in the NRH group ranged from 4.4 to 22.0 kPa with a good correlation with HVPG (r=0.52, p-value = 0.047).

Discussion

Our assumption that LSM is normal in all patients with PVT was not observed in the current study as abnormal LSM was present in up to one-third of patients. The abnormal LSM despite lack of fibrosis in the PVT group is likely due to its increase from an elevated FHVP. The wide variation of LSM in NRH group may reflect the severity of NRH. Our findings are similar to one other study that reported a wide range of LSM discouraging its role in diagnosing patients with NCPH.[2] It has been suggested that in NRH, the pre-sinusoidal portal hypertension is related to obliterative portal venopathy while the sinusoidal portal hypertension is related to sinusoidal obstruction due to compression by regenerative nodules.[3] In the current study, we found a good correlation between LSM and HVPG and likely indicative of the severity of NRH and underlying portal HTN. It is therefore conceivable that early in the course of NRH, the HVPG may be low primarily due to pre-sinusoidal portal hypertension.[4] It is also possible that the variation in LSM in NRH is reflective of the predominant mechanism of injury (i.e., low LSM in pre-sinusoidal vs. high LSM in sinusoidal portal hypertension).[4] Evaluating the use of VCTE in the diagnostic workup of NCPH is a challenging topic to approach due to rarity and heterogeneity of the etiology due to varied chronicity, severity, and etiologies. *From a cohort of cirrhotic patients that underwent upper endoscopy and VCTE, we identified control patients after matching for presence of esophageal varices (Supplementary Table 1). As anticipated the LSM values in the cirrhosis cohort were statistically significantly higher (26.6 ± 18.4 vs. 13.2 ± 11.5 kPa, P- value = <0.001).* Some limitations of the current study are the sample size and lack of single operator for the measurement of LSM and portal pressures. In summary, although intuitively appealing, the use of VCTE as a diagnostic tool to differentiate liver disorders associated with NCPH from cirrhosis and PVT from other causes of NCPH is fraught with complexities and LSM

must be interpreted with caution in patients with NCPH.

Table 1. Select demographic, blood test parameters, liver histology, portal pressure measurements and liver stiffness measurement in the study cohort. All values are reported as mean ± SD unless otherwise reported.

	NRH (n=22)	PVT (n=13)	Miscellaneous (n=8)	Total cohort (N=43)
Demographics				
Age	61 ± 13	51 ± 12	53 ± 18	56 ± 14
Male (%)	64	46	13	50
Caucasian (%)	91	92	88	90
BMI (kg/m^2)	27 ± 4	30 ± 6	30 ± 6	28 ± 5
Blood tests				
Total bilirubin (mg/dL)	1.3 ± 1.1	1.2 ± 0.8	2.4 ± 2.6	1.5 ± 1.5
ALT (U/L)	41 ± 65	32 ± 36	26 ± 15	35 ± 50
Platelet count (k/mm^3)	178 ± 146	167 ± 100	269 ± 158	193 ± 139
INR	1.1 ± 0.2	1.4 ± 0.6	1.7 ± 1.2	1.4 ± 0.7
Varices (%) (n=34)	72	75	75	74
METAVIR Fibrosis Stage (n=38)				
None (%)	50	62	50	52
F1 (%)	9	23	0	12
F2 (%)	27	0	38	21
F3 (%)	0	0	13	2.4
F4 (%)	0	0	0	0
Not available (%)	14	15	0	12
Trans-jugular portal pressure measurements (n=33)				
RA (mmHg)	4 ± 3	5 ± 4	5 ± 3	5 ± 3
FHVP (mmHg)	6 ± 2	9 ± 4	8 ± 4	7 ± 4
WHVP (mmHg)	13 ± 6	13 ± 5	19 ± 5	14 ± 6
HVPG (mmHg)	7 ± 5 (n=15)	4 ± 2 (n=11)	11 ± 7 (n=7)	7 ± 5
Transient elastography				
LSM (kPa)	11.0 ± 5.3	8.4 ± 5.4	26.7 ± 19.7	13.1 ± 11.5
Minimum-Maximum (kPa)	4.4 - 22.0	3.6 – 18.8	7.4 – 67.8	3.6 – 67.8
LSM >6.5 kPa (%)	68	39	100	65
*Abnormal LSM (%)	50	31	75	49

RA: right atrium; FHVP: free hepatic vein pressure; WHVP: wedge hepatic vein pressure; HVPG: Hepatic vein pressure gradient; LSM: liver stiffness measurement. Etiologies in "Miscellaneous" category included sarcoidosis, Budd-Chiari, acute fatty liver pregnancy, and lymphoma. *Abnormal LSM is defined based on LSM >10 kPa indicative of compensated advanced chronic liver disease (cACLD) (Baveno VI recommendations).

References:

1. Non-cirrhotic portal hypertension. Lancet 1981;2:1267-8.
2. Laharie D, Vergniol J, Bioulac-Sage P, et al. Usefulness of noninvasive tests in nodular regenerative hyperplasia of the liver. Eur J Gastroenterol Hepatol 2010;22:487-93.
3. Duseja A, Chawla Y. Portal hypertension in nodular regenerative hyperplasia: a mixed bag! J Gastroenterol Hepatol 2012;27:1260-2.
4. Ghabril M, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. Semin Liver Dis 2014;34:240-5.

Figure Legend

Figure 1. Flowchart of patients with NCPH in the study cohort. The ranges of LSM in each cohort and the proportion of patients with abnormal LSM are also mentioned. "Miscellaneous" category included sarcoidosis, Budd-Chiari, acute fatty liver pregnancy, and lymphoma. Abbreviations: LSM: Liver Stiffness Measurement; cACLD: Compensated advanced chronic liver disease; NRH: Nodular Regenerative Hyperplasia; PVT: Portal Vein Thrombosis